H. pylori Treatment
Therapeutic Class Review (TCR)

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FDA-APPROVED COMBINATION PRODUCTS

Drug	Manufacturer	Indication
bismuth subsalicylate, metronidazole, tetracycline (Helidac®)[1]	Prometheus	Components are indicated in combination with a histamine type 2-receptor (H2) antagonist for the treatment of patients with *Helicobacter pylori (H. pylori)* infection and duodenal ulcer disease to eradicate *H. pylori*.
omeprazole, amoxicillin, clarithromycin (Omeclamox-Pak™)[2]	Pernix	Components are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to one-year history) to eradicate *H. pylori*.
lansoprazole, amoxicillin, clarithromycin (Prevpac®)[3]	generic, Takeda	Components are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.
bismuth subcitrate potassium, metronidazole, tetracycline (Pylera®)[4]	Aptalis	Components are indicated in combination with omeprazole for the treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*. Omeprazole should be taken with the breakfast dose and dinner dose of Pylera.

OVERVIEW

Although the traditional theories regarding the pathogenesis of peptic ulcers focus on acid hypersecretion, this finding is not universal, and it is now known that hypersecretion is not the primary mechanism by which most ulceration occurs.[5] It appears that certain factors, such as *Helicobacter pylori* (*H. pylori*) and nonsteroidal antiinflammatory drugs (NSAIDs), disrupt the normal mucosal defense and repair, making the mucosa more susceptible to the attack of acid.

The mechanisms by which *H. pylori* causes mucosal injury are not entirely clear, but several theories have been proposed.[6,7] Urease produced by the organism catalyzes urea to ammonia. Ammonia, while enabling the organism to survive in the acidic environment of the stomach, may erode the mucous barrier, leading to epithelial damage. Cytotoxins produced by *H. pylori* have also been implicated in host epithelial damage. Mucolytic enzymes (e.g., bacterial protease, lipase) appear to be involved in degradation of the mucous layer, making the epithelium more susceptible to acid damage. Lastly, cytokines produced in response to inflammation may play a role in mucosal damage and subsequent ulcerogenesis.

H. pylori is associated with intestinal-type adenocarcinoma of the gastric body and antrum. Infected persons are 3 to 6 times more likely to develop stomach cancer. Gastric lymphomas and mucosa-associated lymphoma tissue (MALT) lymphomas have also been linked to this infection.[8] As many as two-thirds of high-grade MALT lymphomas may respond to antibiotic therapy for *H. pylori*.[9]

Eradication of *H. pylori* has been shown to decrease peptic ulcer disease (PUD).[10] Several studies have shown that eradication of *H. pylori* is more cost-effective than continuous therapy with acid suppression agents, such as histamine type 2 receptor (H2) antagonists or proton pump inhibitors (PPIs).[11,12,13] Long-term treatment with H2 antagonists or PPIs reduces the risk of recurrence proportionally to the amount of acid suppression achieved. One year relapse rate for gastric and duodenal ulcers is more than 60% after cessation of these traditional antiulcer therapies. The rate of

ulcer recurrence is considerably lower after *H. pylori* eradication therapy (less than 10%). Recurrent infections are usually due to persistent *H. pylori*, which, if documented, should be treated with a second course of *H. pylori* eradication therapy.

H. pylori eradication consists of multiple drug therapy that combines antibiotics with an acid-suppressive agent (H2 antagonists or PPI) for 7 to 14 days. Although no regimen offers 100% eradication, it appears that dual drug and short-term therapy result in lower eradication rates, compared with triple drug regimens lasting 10 to 14 days.[14,15,16,17,18] Medication compliance, medication-related adverse effects, and antimicrobial resistance may also affect eradication.[19,20]

The 2007 American College of Gastroenterology (ACG) guidelines recommend 10 to 14 days of a triple-drug regimen containing a PPI, clarithromycin, and either amoxicillin or metronidazole.[21] Although 10 to 14 days is recommended, the ACG also indicates that giving therapy for 2 weeks may be preferred. In addition, these guidelines state that recent studies suggest the eradication rates achieved by first line therapy with a PPI, clarithromycin, and amoxicillin have decreased to 70% to 85%, in part due to clarithromycin resistance. An update to these guidelines is in progress, but an anticipated publication date has not been released.[22] Triple therapy using a PPI, clarithromycin, and either amoxicillin or metronidazole for 14 days is also recommended as first line therapy in the 2006 global update to the Maastricht III Consensus Report.[23] Bismuth containing quadruple therapy is also a first choice treatment option.

The 4 packaged combination products available will be included in this review. PPIs are addressed in a separate review, although dosing for those with approval for *H. pylori* eradication (in combination with other agents) is included within this review.

PHARMACOLOGY[24,25,26,27]

PPIs suppress acid and induce rapid ulcer healing. Increased gastric pH accompanying their use can enhance tissue concentration and efficacy of antimicrobials, creating a hostile environment for *H. pylori*.

Bismuth subsalicylate, metronidazole, clarithromycin, and tetracycline individually have demonstrated in vitro activity against most susceptible strains of *H. pylori*. Metronidazole resistance occurs most often in patients previously treated with metronidazole, primarily younger women who are more likely to have had prior exposure to the antibiotic.[28,29] Studies have reported *H. pylori* resistance rates to metronidazole of 29.1% to 41%.[30] Clarithromycin resistance is not as common (occurrence of 4.1% to 15%) and occurs most often in older, female, and inactive ulcer patients.[31,32] Primary amoxicillin resistance is very rare (1.4%).[33] Successful eradication of *H. pylori* is affected more by the presence of resistance to clarithromycin than to metronidazole.[34,35,36] It would appear that short regimens that include metronidazole may be subject to a reasonably high failure rate, particularly in young women.

In a study of the effect of differing therapies on the development of resistance, dual therapy with the combination of a PPI and clarithromycin resulted in 88.9% of the patients acquiring clarithromycin resistance. With triple therapy, percentages of patients acquiring clarithromycin-resistant strains after using PPI + clarithromycin + amoxicillin or PPI + clarithromycin + metronidazole were 38.7% and 90%, respectively ($p<0.01$).[37] These data suggest that regimens containing amoxicillin may prevent the selection of secondary clarithromycin resistance.

PHARMACOKINETICS[38,39,40,41]

Pharmacokinetics for Helidac, Omeclamox-Pak, and Prevpac, when all of their components are co-administered, have not been studied. Please consult the individual package inserts for full details.

A comparative pharmacokinetic bioavailability study of Pylera found similar pharmacokinetic parameters for the individual drugs when administered as separate capsule forms or as Pylera. A second pharmacokinetic evaluation showed that food reduces the systemic absorption of all 3 Pylera components: metronidazole by 6%, tetracycline by 34%, and bismuth by 60%. This reduction in absorption is not considered to be clinically significant.

CONTRAINDICATIONS/WARNINGS[42,43,44,45]

All products in this category carry a warning and contraindication for any patients with known hypersensitivity to any of the components of the differing formulations. These hypersensitivity reactions may be expressed as anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, or urticaria.

Concomitant administration of Prevpac with any of the following drugs is contraindicated: cisapride, pimozide, ergotamine, or dihydroergotamine. There have been post-marketing reports of cardiac arrhythmias and even fatalities as a result of some of the aforementioned drug interactions.

Omeclamox-Pak is contraindicated when a hypersensitivity to omeprazole, any macrolide antibiotic, any penicillin, or any component of the formulations exists. Additionally, Omeclamox-Pak should not be co-administered with pimozide, ergotamine, or dihydroergotamine.

Omeclamox-Pak and Prevpac both carry a warning for the potential development of acute interstitial nephritis (AIN) which has been observed in patients taking proton pump inhibitors (PPIs). AIN may occur at any time during PPI therapy and has been attributed to an idiopathic hypersensitivity reaction. Should AIN develop, the use of PPI therapy should be immediately discontinued.

H. pylori treatments may contain a penicillin-type antibiotic. Serious and occasionally fatal anaphylactic reactions have occurred when patients are hypersensitive to penicillins, including amoxicillin and even some cephalosporins. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillin therapy. This type of reaction is more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Serious reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation.

Clarithromycin should not be administered in pregnant women except in clinical circumstances where no alternative treatment option is appropriate. Additionally, *H. pylori* products containing clarithromycin (Omeclamox-Pak, Prevpac) should not be given concomitantly with HMG-CoA reductase inhibitors (statins) which are extensively metabolized by CYP3A4 pathways (e.g., lovastatin or simvastatin), as this may result in an increased risk of myopathy including rhabdomyolysis.

It should also be noted that Helidac carries a black box warning because of the known ability of metronidazole to be carcinogenic in mice and rats. Metronidazole use should be reserved for approved conditions (*H. pylori* being one of them). As of January 2011, the black box warning was removed from the prescribing information for Pylera.[46,47] There is also the added concern of *H. pylori* resistance with metronidazole. It is probably best to reserve combinations containing metronidazole to patients with allergies to clarithromycin or amoxicillin or who have failed therapies with those other antibiotics.

The concurrent use of Helidac in patients receiving methoxyflurane therapy is contraindicated as this may result in fatal renal toxicity. Helidac is also contraindicated in patients receiving disulfiram therapy within two weeks of being administered Helidac. Psychotic reactions have been reported in patients due to a disulfiram-like reaction due to the metronidazole component of Helidac.

Prescribing any antibiotic-containing *H. pylori* treatment in the absence of a proven or strongly suspected bacterial infection, or for a prophylactic indication, is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Helidac is contraindicated in the following patient populations: pregnant or nursing women, pediatric patients, patients with renal or hepatic impairment, and patients with a known hypersensitivity to any of its component ingredients or aspirin/salicylate allergies.

DRUG INTERACTIONS[48,49,50,51]

All drug interactions are the same as for the individual agents. Consult prescribing information for full details.

ADVERSE EFFECTS[52,53,54,55]

Drug	Abdominal pain	Diarrhea	Headache	Nausea	Melena	Altered taste
bismuth subsalicylate, metronidazole, tetracycline (Helidac)	6.8	6.8	1.5	12	3	nr
omeprazole, amoxicillin, clarithromycin (Omeclamox-Pak)	2 – 5.2	14	7	4	nr	10
lansoprazole, amoxicillin, clarithromycin (Prevpac)	<3	7	6	<3	nr	5
bismuth subcitrate potassium, metronidazole, tetracycline (Pylera) + omeprazole	8.8	8.8	8.2	8.2	nr	4.8

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and should not be considered comparative or all inclusive. nr= not reported.

SPECIAL POPULATIONS[56,57,58,59]

Pediatrics

Effectiveness of a 1-week, non-bismuth quadruple therapy was studied prospectively in children with proven *H. pylori* infection in a population with a high rate of metronidazole resistance.[60] *H. pylori*-positive children were treated with omeprazole, clarithromycin, amoxicillin, and metronidazole for 7 days. The result of treatment was assessed 1 month after treatment with endoscopy and biopsy. The same treatment was repeated for 2 weeks if *H. pylori* was still present. In patients who needed a third endoscopy, their biopsy specimens were cultured to determine antibiotic sensitivity. Results were correlated with patients' symptoms and endoscopic findings. Thirty-three children with acute (severe epigastric pain, n=14; gastrointestinal bleeding, n=9) and chronic (recurrent abdominal pain, n=7; anemia, n=3) conditions were treated for *H. pylori*. Thirty-one (94%) were confirmed to have *H. pylori* eradicated by 1 week of therapy, whereas 1 patient had eradication after a further 2 weeks of therapy (3.3%). The only unresponsive patient had *H. pylori* isolate resistant to both clarithromycin and metronidazole. All ulcers and erosions healed after the eradication of *H. pylori*. Three patients had persistent recurrent abdominal pain despite *H. pylori* eradication.

Pregnancy

Omeclamox-Pak and Prevpac are both Pregnancy Category C, and Helidac and Pylera are Pregnancy Category D.

Other Considerations (e.g., Renal, Hepatic)

Helidac and Pylera combinations are contraindicated in severe hepatic and renal insufficiency. Omeclamox-Pak is not recommended in hepatic impairment. With severe hepatic insufficiency, a dose reduction of Prevpac is recommended, and its use is not recommended with a creatinine clearance (CrCL) less than 30 mL/min. Prolonged clarithromycin dosing intervals may be appropriate for Omeclamox-Pak in the presence of severe renal impairment with or without coexisting hepatic impairment.

DOSAGES[61,62,63,64,65]

Drug	Dosage	Additional Medications Required	Duration (days)	Availability
Helidac	metronidazole 250 mg + tetracycline 500 mg + bismuth subsalicylate 525 mg, each given 4 times a day	H2 receptor antagonist	14	14 blister cards, each containing: ▪ 8 bismuth subsalicylate 262.4 mg chewable tablets ▪ 4 metronidazole 250 mg tablets ▪ 4 tetracycline 500 mg capsules
Omeclamox-Pak	omeprazole 20 mg + amoxicillin 1 gm + clarithromycin 500 mg, each given twice a day	omeprazole 20 mg once daily for 18 days if active ulcer is present	10	Individual daily administration pack containing: ▪ 2 omeprazole 20 mg capsules ▪ 4 amoxicillin 500 mg capsules ▪ 2 clarithromycin 500 mg tablets
Prevpac	lansoprazole 30 mg + amoxicillin 1 gm + clarithromycin 500 mg, each given twice a day	--	10 or 14	Individual daily administration pack containing: ▪ 2 lansoprazole 30 mg capsules ▪ 4 amoxicillin 500 mg capsules ▪ 2 clarithromycin 500 mg tablets
Pylera	Each capsule contains: bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline HCl 125 mg; 3 capsules given 4 times a day	omeprazole 20 mg twice a day	10	The daily dosing pack (10-day therapy pack) is designed to hold: ▪ 12 3-in-1 capsules of Pylera each containing: 140 mg bismuth subcitrate potassium, 125 mg metronidazole in outer capsule and 125 mg tetracycline HCl in inner capsule ▪ 2 omeprazole 20 mg capsules
esomeprazole (Nexium®)	esomeprazole magnesium 40 mg daily	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10	esomeprazole magnesium: 20 mg, 40 mg delayed-release capsules 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg delayed-release powder for oral suspension esomeprazole strontium: 24.65 mg and 49.3 mg delayed-release capsules of esomeprazole strontium (equivalent to 20 mg and 40 mg of esomeprazole, respectively)

Dosages (continued)

Drug	Dosage	Additional Medications Required	Duration (days)	Availability
lansoprazole (Prevacid®)	lansoprazole 30 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10 to 14	15 mg, 30 mg delayed-release capsules 15 mg, 30 mg delayed-release orally disintegrating tablets
	lansoprazole 30 mg 3 times a day	amoxicillin 1,000 mg 3 times a day	14	
omeprazole (Prilosec®)	omeprazole 20 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10 (14 days recommended by ACG)	10 mg, 20 mg, 40 mg delayed-release capsules 2.5 mg, 10 mg packets for oral suspension Continue with omeprazole 20 mg daily for 14 days in patients with active ulcer
	omeprazole 40 mg daily	clarithromycin 500 mg 3 times a day	14	
rabeprazole (Aciphex®)	rabeprazole 20 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	7	20 mg delayed-release tablets

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the trials with agents in this class were performed over a very short duration of treatment and in an open-label manner; introduction of bias must be considered when evaluating study findings.

lansoprazole, amoxicillin, and clarithromycin (Prevpac) for 10 days versus 14 days

A multicenter, randomized, controlled, double-blind U.S. trial with 236 patients evaluated the efficacy of triple therapy (lansoprazole 30 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg) given twice daily for 10 days versus 14 days in the eradication of *H. pylori*.[66] There was no statistical difference in efficacy between the 10-day group (84% eradication) and the 14-day group (85% eradication). Adverse effects between the groups were similar.

A randomized, multicenter, prospective trial compared triple combination therapy (omeprazole 20 mg or an equivalent dose of a PPI, amoxicillin 1,000 mg and clarithromycin 1,000 mg) for 7 days versus 14 days.[67] A total of 598 patients were enrolled (n=337 with 7 day treatment and n=261 with 14 day treatment). The 7-day treatment was not inferior to the 14-day treatment (83.6% for 7 day therapy and 86.6% for 14 day therapy). Adverse events were comparable in both groups.

bismuth, metronidazole, tetracycline (Pylera) with omeprazole versus triple therapy

In an open-label, multicenter, parallel group, active-controlled trial, the quadruple therapy of bismuth subcitrate potassium 1,680 mg daily, metronidazole 1,500 mg daily, and tetracycline 1,500 mg daily (Pylera) with omeprazole 20 mg twice daily had similar efficacy as the active control triple therapy of clarithromycin 500 mg daily, amoxicillin 1,000 mg daily, and omeprazole 20 mg twice daily in the treatment of *H. pylori*-positive adults with current duodenal ulcer or a history of duodenal ulcer disease.[68] Eradication rates were 87.7% for quadruple therapy and 83.2% for the active control triple therapy. Gastrointestinal adverse events were similar for both arms.

COMPARATIVE EFFICACY (FOR FDA-APPROVED REGIMENS)

Drug	Duration (days)	Eradication Rates (%)
Helidac[69]	14	77 – 82*
Omeclamox-Pak[70]	10	90**
Prevpac[71,72,73]	10 or 14	80 – 95.2
Pylera[74]	10	87.7
esomeprazole (Nexium)[75]	10	84 – 85
lansoprazole (Prevacid)[76,77,78]	10 – 14	80 – 95.2
	14	77
omeprazole (Prilosec)[79,80,81,82]	10 (14 days recommended by ACG)	69 - 90
	14	77 – 95
rabeprazole (Aciphex)[83]	7	77.3 – 84.3

*An unapproved regimen similar to Helidac using omeprazole 20 mg twice daily rather than an H2 antagonist had an eradication rate of 90% to 99%.[84]

** Patients with an active duodenal ulcer who received the 10-day regimen plus 18 additional days of omeprazole 20 mg therapy daily had an eradication rate of 77% to 78%.[85]

META-ANALYSES

A meta-analysis evaluated randomized clinical trials comparing PPIs to H2 antagonists with the same antibiotics.[86] Twenty studies fulfilled the inclusion criteria. In the intention-to-treat analysis, the mean eradication rates with PPIs and H2 antagonists plus antibiotics were 74% and 69%, respectively. The analysis concluded that, overall, PPIs were more effective than H2 antagonists when prescribed at usual doses with antibiotics to eradicate *H. pylori* infection.

Triple therapy (PPI, clarithromycin, and amoxicillin or an imidazole) is the first-line treatment for *H. pylori* infection.[87,88] Quadruple therapy (PPI, tetracycline, metronidazole, and a bismuth salt) is a very effective regimen even in areas of high prevalence of antibiotic resistance.[89] To compare triple versus quadruple therapy for the first-line treatment of *H. pylori* infection, an extensive literature search identified randomized trials comparing triple versus quadruple therapy. Four studies met the inclusion criteria. Eradication rates with quadruple therapy were slightly higher for both the intention-to-treat (81% versus 78%) and the per protocol analyses (88% versus 85%). The differences were not statistically significant.

A systematic evaluation as to whether sequential treatment eradicates *H. pylori* infection better than standard triple therapies and compare the risk of adverse events with these 2 regimens was conducted.[90] A comparison of studies evaluating the efficacy of the 10-day sequential therapy versus standard triple regimens for eradication of *H. pylori*, and the pooled risk ratios (RR) and 95% confidence intervals (95% CI) were calculated for 11 randomized trials. Pooled analyses demonstrated clear superiority of the sequential therapy over 7-day triple regimen with an RR of 1.23 (95% CI, 1.19 to 1.27), and over 10-day triple regimen with a RR of 1.16 (95% CI, 1.1 to 1.23). Adverse event rates were similar for sequential therapy versus 7-day triple therapies, RR of 0.96 (95% CI, 0.7 to 1.31). In

conclusion, sequential therapy was associated with a higher eradication rate of *H. pylori* compared with both 7-day triple regimen and 10-day triple regimen.

SUMMARY

Triple and quadruple drug regimens are more effective at eradicating *H. pylori* than dual drug regimens. The most effective FDA-approved regimens are those that combine a PPI with amoxicillin and clarithromycin. This is likely due to the highly effective acid suppression provided by the PPI (in comparison to an H2 antagonist) and the low rate of resistance to the 2 antibiotics (in comparison to metronidazole). These factors may reduce the usefulness of the combination product Helidac because of the required concomitant use of an H2 antagonist.

The 2007 American College of Gastroenterology (ACG) guidelines recommend 10 to 14 days of a triple-drug regimen containing a PPI, clarithromycin, and either amoxicillin or metronidazole. An update to these guidelines is in progress.

The other triple combination products, Omeclamox-Pak and Prevpac, combine the most effective components of triple therapy including a PPI. Omeclamox-Pak is intended as a 10-day course of therapy while Prevpac is a 14-day regimen. The combination therapy, Pylera along with omeprazole, offers quadruple drug therapy with competitive eradication rates compared to other triple drug regimens. Pylera may have a place in therapy for those patients who are allergic to amoxicillin or clarithromycin or in whom bacterial resistance is known or suspected. Omeclamox-Pak or Prevpac may be better suited for special populations such as pediatrics, pregnancy, and renal insufficiency. Finally, Prevpac may be suitable for use in patients with hepatic impairment.

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